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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,032	02/09/2005	Chise Mukaidani	2004 1544A	1374

513 7590 11/17/2006

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ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/509,032	MUKAIDANI ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *3-6,12-15,19-21 and 23-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-11 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/22/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-2, 7-11, and 16-18, in the reply filed on 8/16/2006 is acknowledged.

Claims 3-6, 12-15,19-21, and 23-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/16/2006.

The preliminary amend dated 9/27/2004 was entered. Claims 1, 3, 6, 10, 12, 15, 21, 23, 24, 27, 30, and 33 are amended. Claim 22 is cancelled. Claims 1-21 and 23-33 are pending. Claims 1-2, 7-11, and 16-18 are under consideration.

Information Disclosure Statement

2. The information disclosure statement (IDS) was filed on 2/22/2005. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

The information disclosure statement filed 9/24/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The examiner was able to retrieve and consider the U.S. patents and WO documents listed, but copies of the non-patent literature documents could not be located.

Applicant did not provide non-patent literature reference AP on sheet 1 of the IDS. Therefore it was not considered.

The information disclosure statement (IDS) was filed on 9/24/2004. The submission is not in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is not being fully considered by the examiner. References AJ and AM on Sheet 1 of the IDS were not considered because they were in a language other than English.

Priority

3. Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Although priority papers have been submitted in the instant case, a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. Therefore, the effective filing date is 3/25/2003, the teachings of Dandri et al. (April 2001) are applicable against the instant claims (see following rejections under 35 USC 102(b)).

Claim Objections

4. Claim 1 and 10 objected to because of the following informalities: Claims 1 and 10 recite "a liver of an immunodeficient hepatopathy mouse" on line 2 of claim 1 and

lines 3 and 4 of claim 16. The recitation of "a liver" suggests that the mouse can have more than one liver and should read "the liver". Appropriate correction is required.

Claim 10 is objected to because of the following informalities: Lines 12-14 of the claim recite, "wherein the mouse transplanted with the human hepatocytes is fed under such a condition as being protected from the attack by human complement produced by the human hepatocytes transplanted therein." This is redundant with a similar recitation in lines 10-11. Appropriate correction is required.

Claims 7 and 16 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claims require that the method use proliferative human hepatocytes. The specification teaches that a "proliferative human hepatocyte" has the ability to proliferate in vitro (p. 19, line 16-26), which suggests that they have the ability to proliferate before transplantation. Therefore, the instant method of proliferating human hepatocytes would inherently use human hepatocytes that are proliferative. Therefore these claims do not further limit the parent claims.

Claims 8 and 17 are objected to for their recitation of "hepatocytes which proliferate with colony". This is grammatically incorrect. If the recitation is supposed to refer to one colony it should recite "a" "colony". If it is to refer to multiple colonies, the recitation should recite "colonies". Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

5. Claim(s) 1-2, 7-11, and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention is drawn to a method of proliferating human hepatocytes comprising transplanting human hepatocytes into the liver of an immunodeficient mouse and proliferating said hepatocytes in the mouse liver wherein the mouse transplanted with human hepatocytes is fed under such conditions as being protected from the attack by human complement by the human hepatocytes. The invention is also drawn to a method of proliferating human hepatocytes comprising (1) a step of transplanting human hepatocytes into the liver of immunodeficient hepatopathy mouse, (2) a step of isolating the proliferated human hepatocytes from the mouse liver, and (3) a step of a step of transplanting human hepatocytes into the liver of immunodeficient hepatopathy mouse. Narrowing embodiments specify that the protection again human complement encompass administering a complement inhibitor or using progeny that have been produced by crossing a DAF transgenic mouse and an immunodeficient hepatopathy

mouse for the mouse to receive the transplant. Other narrowing embodiments specify that the human hepatocytes be proliferative human hepatocytes recognized by a monoclonal antibody specific for human hepatocytes.

When the claims are analyzed in light of the specification, the instant invention encompasses feeding anything under conditions as being protected from the attack by human complement and administering any complement inhibitor. However, the specification teaches only a single complement inhibitor, Futhan, and does not teach the full breadth of feeding conditions that result in protection from the attack of human complement encompassed by the claims. In analyzing whether the written description requirement has been met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. While the specification teaches administration of 200 μl of Futhan at a concentration of 2 mg/ml(p. 35, lines 13-15), the specification fails to disclose any other complement inhibitors or feeding anything that would result in protection from human complement. Therefore because the specification only discloses one species, Futhan for a complement inhibitor, the specification does not teach the complete structure of a representative number of species of the claimed genus that comprises feeding anything under conditions as being protected from the attack by human complement and administering any complement inhibitor.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant characteristics, specified features and functional attributes that would distinguish different members of the claimed genus. The

specification discloses that the transplanted human hepatocytes were producing human C3 and that in they treated with Futhan (p. 35, lines 10-15). However, this does not specifically disclose any special identifying features/characteristics that would distinguish the species of the genus comprising feeding anything under conditions as being protected from the attack by human complement and administering any complement inhibitor. Therefore, a representative number of species have not been sufficiently described by other relevant characteristics, specified features and functional attributes in the specification as required by the written description requirement.

In conclusion, given the breadth of the genus, species have not been sufficiently described by other relevant characteristics, specified features and functional attributes, and the limited number of examples provided, and given that no specific identifying features/characteristic of species of the genus, were provided, the written description requirement disclosing the complete structure of genus comprising feeding anything under conditions as being protected from the attack by human complement and administering any complement inhibitor has not been met. Furthermore, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of the genus comprising feeding anything under conditions as being protected from the attack by human complement and administering any complement inhibitor, at the time the application was filed.

Scope of Enablement

6. Claims 1-2, 7-11, and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of proliferating human hepatocytes comprising transplanting proliferative human hepatocytes into the liver of a uPA-Tg/SCID immunodeficient hepatopathy mouse comprising a homozygous insertion of a uPA-Tg into the genome of a homozygous SCID mouse, administering an effective amount of the complement inhibitor, Futhan, to protect against tissue damage associated with human complement produced by human hepatocytes, proliferating said human hepatocytes in the liver of said mouse, isolating human hepatocytes from the liver of said mouse transplanted with human hepatocytes, and transplanting the human hepatocytes isolated from the liver of said mouse into other uPA-Tg/SCID immunodeficient hepatopathy mice comprising a homozygous insertion of a uPA-Tg into the genome of a homozygous SCID mouse, does not reasonably provide enablement for a method comprising transplanting non-proliferative at all and does not enable transplanting proliferative human hepatocytes into the liver of an immunodeficient hepatopathy mouse or an immunodeficient hepatopathy mouse administered any complement inhibitor by any method including feeding or a progenitor mouse obtained by mating between an immunodeficient hepatopathy mouse and a decay-accelerating factor (DAF/CD55) transgenic mouse, proliferating said human hepatocytes in the liver of said mouse, isolating human hepatocytes from the liver of said mouse transplanted with proliferative human hepatocytes, and transplanting the human hepatocytes isolated from the liver of said mouse into any other immunodeficient hepatopathy mice, or an

immunodeficient hepatopathy mice administered a complement inhibitor or progenitor mice obtained by mating between an immunodeficient hepatopathy mice and a decay-accelerating factor (DAF/CD55) transgenic mice. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use/make the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification discloses the production of a immunodeficient hepatopathy mouse by mating and backcrossing UPA-Tg transgenic mice and CB-17/Icr Scidjcl

SCID mice to produce a mouse (uPA-Tg/SCID) that is homozygous for an insertion of uPA-Tg into its genome and is also homozygous mutant for the SCID gene (p. 32, lines 6-16). The specification discloses a method of transplanting human hepatocytes into the liver of 14 to 48 day-old, uPA-Tg/SCID mice (p. 33, lines 26-30 and p. 34, lines 1-10). The specification discloses that because uPA-Tag/SCID mice that received the human hepatocyte transplant were becoming moribund and death due to internal bleeding, they began to treat human hepatocyte transplanted uPA-Tg/SCID mice with the complement inhibitor, Futhan (p. 35, lines 7-15). Treatment with an effective amount of a complement inhibitor, Futhan, allowed the mice to live for long periods and overall mice that received the inhibitor faired better than mice that did not receive complement inhibitor (p. 35, 21-24). The specification discloses that a steady increase in human albumin concentration in the sera of mice that received human hepatocyte transplants (see figures 1-3), suggestive of an increased human hepatocyte number and proliferation. The specification also teaches a method of collecting human hepatocytes from the mouse liver by subjecting the excised livers to collagenase perfusion and separating the human hepatocytes form the mouse hepatocytes uses a human hepatocyte specific monoclonal antibody from hybridoma K8216 and subjecting the hepatocytes to FACS analysis (par bridging p. 38 and 39). Human hepatocytes isolated from the mouse livers were re-transplanted into the livers of other uPA-Tg/SCID mice using the same methods as disclosed above (p. 39, lines 12-14). In re-transplantation, human albumin levels increase in some of the mice but not to the same extent as seen in the first transplantation, suggesting that the second round of

transplantation results in proliferation of hepatocytes but the extent of proliferation was limited compared to the first round (see Figure 11). The specification also discloses that the monoclonal antibody produced from the mouse-mouse K8223 (deposition number: FERM BP-8334) was used to separate human hepatocytes by FACS analysis and demonstrated similar reactivity to the monoclonal antibodies produced by K8216, which was described in the transplantation studies (p. 43, lines 22-28).

However, the art teaches that the development of mouse models comprising a chimeric liver that will support transplantation of human liver cells, let alone proliferation as is required by the instant methods is challenging and unpredictable. Kneteman et al (US 6,509,514, p.d.-1/21/2003) reports that the development of mice having chimeric livers with human hepatocytes has proven to be no simple matter and the field of xenogeneic liver transplantation has moved very slowly and met with many obstacles (col 2, lines 29-35). Pietschmann and Bartenschlager (Clin Liver Dis 7(1):23-43, 2003) report that one of the challenges is that the hepatopathy mouse models commonly used, such as the homozygous Alb-uPA transgenic mouse or crosses with this mouse, are difficult to use for the production of chimeric mouse with livers containing human hepatocytes, because of the toxicity and side effects of the transgene (see abstract). Kneteman et al also disclose that the phenotype of this transgenic mouse results in a profoundly hypofibrinogenemic state and accelerated hepatocyte death (col 240-43) and therefore timing of transplantation of these mice with human hepatocytes is critical for the repopulation and rescue them from death. Furthermore, Pietschmann and Bartenschlager teach that transplantation surgery itself can be technically challenging

because it must be done a few days after birth of the mouse (see abstract). Turrini et al (Transplant Proceedings 38:1181-1184, 2006) teaches the production of a Alb-uPA/SCID/Bg mouse with a chimeric liver comprising human hepatocytes, which is similar to the methods and mouse model described in the examples of the specification (see materials and methods). However, they state, "the system is still very laborious and, in our hands, resulted in very low efficiency. Even if survival 24 hours after surgery was 74%, decreasing to 64% in the following 2 weeks, only 20% of xenotransplanted mice exhibited some detectable level in sera and only 2% reached a significant repopulation index of more than 50%. There exist several limiting issues in this model (1) the availability of human hepatocytes, (2) the absence of pharmacological control of disease, (3) the possibility of adaptive mutations, (4) the difficulty in performing surgery in newborn animals, and (5) the requirement of immunosuppressant [p. 1183, col1]". Overall, the art at the time of filing and presently suggest that there are many obstacles to overcome in producing a immunodeficient hepatopathic mouse model comprising human hepatocytes in its liver. Again recent art suggests a low level of efficiency producing animals that at least have detectable levels of human hepatocytes maintained in its liver and an even lower percent capable of suboptimally repopulating (i.e.-proliferating) in the mouse liver. Therefore it is clear, that many obstacles and unpredictabilities exit in that art of this methodology.

The specification further demonstrates that the instant methods are challenging, unpredictable, and require very specific parameters to successfully use the instantly claimed method to proliferate human hepatocytes. As disclosed above, to keep the

uPA-Tag/SCID from become moribund at the least or dead, the methods need to rely upon the administration of a complement inhibitor to protect against tissue destruction associated with human complement produced by the human hepatocytes. The specification further disclosed that some mice needed subcutaneous administration of SCID mouse serum to support the growth and maintenance of mouse body (p. 36, lines 9-12).

Therefore, because the instant methodology disclosed in the specification and the art is unpredictable at best and artisan would not know how to sucessfully use a method of human hepatocyte proliferation other than the methods specifically disclosed in the examples of the specification with specifically the uPA-Tg/SCID mouse that have been demonstrated to proliferate human hepatocytes.

One embodiment of the instant invention is drawn to the use a progenitor mouse obtained by mating between an immunodeficient hepatopathy mouse and a decay-accelerating factor (DAF/CD55) transgenic mouse (claims 2 and 11). The specification discloses that hDAF/CD55 transgenic mice have tolerance against human complement (p. 16, lines 28-29). The specification then prophetically discloses that this mouse could be mated with an immunodeficient hepatopathy mouse to produce a progeny that gains tolerance to human complement (p. 16, last par). However, the ability to predict a phenotype of a cross with a transgenic animal is unpredictable as well due to many epigenetic factors that can affect the phenotypic outcome. Given the unpredictabilities associated with the method of using the mouse and obstacles to overcome in the overall method, an artisan would not know how to use or make the instant method with

a mouse that prophetically should result in tolerance to human complement. Furthermore, because the one would not know the phenotype of the claimed progenitor mouse and one would have to determine, first if the resultant cross produces a progeny that is immunodeficient hepatopathic mouse that has increased tolerance to human complement. This level of empirical experimentation would be considered undue.

Another embodiment of the instant invention requires feeding the mouse a complement inhibitor or administering a compliment inhibitor by another means (claims 1 and 2). However, the specification only teaches that mice were administered Futhan and does not teach the route of administration. The art teaches methods of administering Futhan by intravenous injection and post-filing art by the inventors teach intravenous administration of Futhan as well (Tateno et al. Am J Path 165(3):901-912). The specification does not teach a method of feeding any complement inhibitors, including Futhan, and does not teach any other means of providing any other inhibitor. Part of the novelty of this model is the use of a complement inhibitor to produce a better transplant model that will allow for proliferation of the transplanted cells. The art does not teach the added use of a complement inhibitor. Therefore, an artisan would have to look to the specification for guidance on how to use a complement inhibitor in the instant method and which inhibitor to use. The specification does teach the administration of Futhan, however, the specification does not teach a route of administration and therefore would have to rely upon methods disclosed by the art to administer Futhan, which is via intravenous administration. Therefore, an artisan would not know how to make or use the instant invention with any other complement inhibitor or means of

providing a complement inhibitor, such as production of the DAF transgenic immunodeficient hepatopathy mouse as claimed. Therefore the instant claims are only enabled to the administration of the complement inhibitor, Futhan, by means taught in the art, mainly intravenous injection. Applicant should take care in avoiding the introduction of new matter in attempt to overcome the above enablement rejection by claim amendment and should point to support in the specification for any claim amendments.

Another embodiment is drawn to the use of proliferative human hepatocytes in the method (claims 7 and 16). This suggests that broader embodiments of the claims could be done with non-proliferative human hepatocytes. However, if the hepatocytes are non-proliferative, they will not be able to proliferate in a method of proliferating human hepatocytes. Neither specification nor the art teach a method utilizing non-proliferative hepatocytes. Therefore, an artisan would not know how to use the instant method with non-proliferative hepatocytes.

Overall, because of the unpredictabilities of a method of proliferating human hepatocytes in a immunodeficient hepatopathy mouse liver disclosed in the art and the specification, the instant invention is only enabled for the embodiments described in the specification that have been demonstrated to work, which are a method of proliferating human hepatocytes comprising transplanting proliferative human hepatocytes comprising transplanting proliferative human hepatocytes into the liver of a immunodeficient hepatopathy mouse comprising a homozygous insertion of uPA-Tg into its genome and homozygous SCID mouse background, administering an effective

amount of a complement inhibitor to protect against tissue damage associated with human complement produced by human hepatocytes, proliferating said human hepatocytes in the liver of said mouse, isolating human hepatocytes from the liver of said mouse transplanted with proliferative human hepatocytes, and transplanting the human hepatocytes isolated from the liver of said mouse into other immunodeficient hepatopathy mice comprising a homozygous insertion of uPA-Tg into its genome and homozygous SCID mouse background.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2, 8, 9, 11, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 11 recite that "the condition of being protected from the attack...is at least one of the following (a) and (b)" with (a) being administering a complement inhibitor and (b) using a progenitor mouse as the immunodeficient hepatopathy mouse. Claims 2 and 11 are dependent from claims 1 and 10 which recite "wherein the mouse transplanted with the human hepatocytes is fed under such a condition as being protected from the attack...". Claims 1 and 11 require that the condition of being protected in obtained by feeding said mouse. However (b) of claims 2 and 11 obtain the condition of being protected by using a progenitor mouse and not feed as required

by the claims 1 and 10 from which they depend. Therefore, there is an inconsistency and one would not know if the progenitor mouse is to be utilized and fed or just progenitor mouse is meant to be utilized in place of feeding or some other scenario. Therefore the metes and bounds are these claims are vague and indefinite.

Claims 8 and 17 recite, "human hepatocytes which proliferate with forming colony". The metes and bounds of this recitation are indefinite because it is unclear if the human hepatocytes are forming the colonies or if the hepatocytes are proliferating with some other cell that is forming colonies.

Claims 9 and 18 are dependent from claims 8 and 17, which have been deemed indefinite. Therefore, dependent claims 8 and 18 are rendered indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1, 7, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. (Hepatology 31:173-181, 2000).

The instant invention is drawn to a method of proliferating human hepatocytes comprising transplanting human hepatocytes into the liver of an immunodeficient mouse and proliferating said hepatocytes in the mouse liver wherein the mouse transplanted with human hepatocytes is fed under such conditions as being protected from the attack by human complement by the human hepatocytes (claim 1). Narrowing embodiments specify that the human hepatocytes be proliferative human hepatocytes recognized by a monoclonal antibody specific for human hepatocytes (claims 7 and 8).

Brown et al disclose a method comprising transferring immortalized primary human hepatocytes into the livers of mice with combined immunodeficiency SCID Rag-2 deficient mice (abstract). They also disclose that before transferring the hepatocytes into the mouse they were infected with human hepatitis B, a liver pathology-causing agent (abstract). Due to the breadth of the limitation of "hepatopathy mouse", it can encompass any disease related aspect of the liver including the pathology of a hepatocyte disease infection as encompassed by infection of the human hepatocytes with Hepatitis B as disclosed by Brown et al.

Brown et al also disclose that clusters of human hepatocytes were indicative of proliferation of the transplanted cells. They further state that these cells retained proliferative capacity, approximately 5 to 9 divisions within the liver of the recipient mice (p. 179, col 2, lines 5-9 and 12-13). Therefore demonstrating that their method of transplanting human hepatocytes into the liver of an immunodeficient hepatopathy mouse resulted in proliferation of the human hepatocytes and also demonstrated that

the hepatocytes that were transplanted were proliferative as encompassed by the claims 7 and 8.

From the disclosure in the specification, it seems that the recitation, "wherein the mouse transplanted with human hepatocytes is fed under such conditions as being protected from the attack by human complement by the human hepatocytes" (claim 1), is intended to provide an oral administration of a complement inhibitor (p. 35, section 2.4). However, this recitation does not require that an agent that can provide protection against complement be fed to the mouse. Therefore, this recitation can be broadly interpreted as the mouse can be fed anything and keep under conditions as being protected from attack of human complement. Brown et al discloses that all animal use and care conformed to established NIH guidelines (p. 174, 1sr par under material and methods), and therefore inherently these mice were fed and housed in a pathogen free environment, meeting the requirements of this above recitation.

Claim 8 also recites "proliferative human hepatocytes recognized by a monoclonal antibody specific for human hepatocytes". This recitation does not require that the human hepatocytes be recognized by a Mab specific human hepatocytes but that rather a characteristic of the human hepatocytes is that they can be recognized by a Mab specific human hepatocytes. Because this embodiment does not alter the method, it has no patentable weight.

8. Claims 1, 7, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Dandri et al (Hepatology 33:981-988, April 2001).

The instant invention is drawn to a method of proliferating human hepatocytes comprising transplanting human hepatocytes into the liver of an immunodeficient mouse and proliferating said hepatocytes in the mouse liver wherein the mouse transplanted with human hepatocytes is fed under such conditions as being protected from the attack by human complement by the human hepatocytes (claim 1). Narrowing embodiments specify that the human hepatocytes be proliferative human hepatocytes recognized by a monoclonal antibody specific for human hepatocytes (claims 7 and 8).

Dandri et al discloses a method of transferring normal human hepatocytes into the livers of uPA/RAG-2 mice (abstract and p. 982, col 2). As discussed above in the enablement, the uPA transgenic genotype is known to result in a hepatopathy phenotype and the RAG-2 genotype is known to result in an immunodeficient phenotype in the transgenic mouse as encompassed by the claims. Dandri et al also discloses the human hepatocytes were estimated to constitute up to 15% of the uPA/Rag-2 mouse liver and that this is proof that normal human hepatocytes can integrate into the liver and undergo multiple cell divisions (abstract), suggesting that the method results in proliferation of the transplanted human hepatocytes and that the hepatocytes were proliferative as claimed in claims 7 and 8.

From the disclosure in the specification, it seems that the recitation, "wherein the mouse transplanted with human hepatocytes is fed under such conditions as being protected from the attack by human complement by the human hepatocytes" (claim 1), is intended to provide an oral administration of a complement inhibitor (p. 35, section 2.4). However, this recitation does not require that an agent that can provide protection

against complement be fed to the mouse. Therefore, this recitation can be broadly interpreted as the mouse can be fed anything and keep under conditions as being protected from attack of human complement. Dandri et al disclose that mice were house and maintained under pathogen free conditions therefore inherently these mice were fed for the duration of the experiment, meeting the requirements of this above recitation.

Claim 8 also recites "proliferative human hepatocytes recognized by a monoclonal antibody specific for human hepatocytes". This recitation does not require that the human hepatocytes be recognized by a Mab specific human hepatocytes but that rather a characteristic of the human hepatocytes is that they can be recognized by a Mab specific human hepatocytes. Because this embodiment does not alter the method, it has no patentable weight. However, Dandri et al disclose a monoclonal antibody that recognizes human serum albumin specifically and used the measurement of human serum albumin to specifically determine the presence of hepatocytes and their ability to repopulate the mouse liver (p. 982, col 2, last par). Therefore, given the breadth of the recitation, the human hepatocytes are being recognized specifically by a monoclonal human serum albumin antibody as claimed.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

9. Claims 1, 7, and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Kneteman et al (US 6,509,514, filed 3/17/2000).

The instant invention is drawn to a method of proliferating human hepatocytes comprising transplanting human hepatocytes into the liver of an immunodeficient mouse and proliferating said hepatocytes in the mouse liver wherein the mouse transplanted with human hepatocytes is fed under such conditions as being protected from the attack by human complement by the human hepatocytes (claim 1). Narrowing embodiments specify that the protection again human complement encompass administering a complement inhibitor or using progeny that have been produced by crossing a DAF transgenic mouse and an immunodeficient hepatopathy mouse for the mouse to receive the transplant (claim 2). Narrowing also embodiments specify that the human hepatocytes be proliferative human hepatocytes recognized by a monoclonal antibody specific for human hepatocytes (claims 7 and 8).

Kneteman et al disclose a method of that sucessfully transplants human hepatocytes into immunocompromised Alb-uPA mice (Example 1, col 14-16). They disclose mating and backcrossing Alb-uPA mouse to B17/SCID beige mice (col 14 , par 1). They disclose that the Alb-uPA provides the hepatopathy phenotype of the mouse (col 14, par 1) and the SCID background provides immunodeficient phenotype (col 7, par 2 and 3). These methods steps are the same as those disclosed by the instant specification and provide the immunodeficient hepatopathy mouse of the instant claims. They disclose a method of transplanting the human hepatocytes into the liver of said mouse intrasplenic injection (col 14, par 2 and 3). They also disclose that 4 weeks after

transplantation the human hepatocytes were identified using a monoclonal specific antibody specific for human MHC class I (col 15, par 3) and determined that the percentage of human hepatocytes had increased from 20 to 60% of the total surface area (col 15, lines 57-60). They further disclosed that human hepatocytes grew in nodules which is indicative of clonal expansion of the cells (col 15, lines 63-67 and col 16, line 1). The demonstration that monoclonal MHC I specifically identified the human hepatocytes encompasses the limitations of human hepatocytes recognized by a monoclonal antibody specific for human hepatocytes which proliferate with forming colony" as claimed in claim 8. Because the monoclonal MHC antibodies are not recognizing any other cells in the mouse other than the human hepatocytes, this encompasses a monoclonal antibody that is specific for human hepatocytes as claimed and because the cells for nodules, this encompasses human hepatocytes that proliferate forming colonies as encompassed by the claims (claim 8).

From the disclosure in the specification, it seems that the recitation, "wherein the mouse transplanted with human hepatocytes is fed under such conditions as being protected from the attack by human complement by the human hepatocytes" (claim 1), is intended to provide an oral administration of a complement inhibitor (p. 35, section 2.4). However, this recitation does not require that an agent that can provide protection against complement be fed to the mouse. Therefore, this recitation can be broadly interpreted as the mouse can be fed anything and keep under conditions as being protected from attack of human complement. Kneteman et al. disclose that mice were house and maintained under pathogen free conditions therefore inherently these mice

were fed for the duration of the experiment, meeting the requirements of this above recitation (col 14, par 1).

Examiner's Comment

10. The invention of the instant application is disclosed in a post-filing art by the inventors (Tateno et al. Am J Path 165(3):901-912, 2004), further demonstrating reduction to practice.

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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